UNIVERSITY OF WASHINGTON
CONSENT FORM

Non-Invasive Electrical Stimulation Therapy for Epilepsy

Principal (Lead) Investigator:
Mark D. Holmes MD
Professor, Neurology
Regional Epilepsy Center
University of Washington
206-744-3576

Assistant Investigator:
Mackenzie Wise BS
Electroneurodiagnostic Technologist 1
Regional Epilepsy Center
University of Washington
206-744-3023

24-hour emergency telephone number with name or position:

Mark D. Holmes MD (Lead Researcher) or on-call epilepsy provider at 206-744-3576.

Researchers' statement

We are asking you to participate as one of twenty subjects in a safety and feasibility study that examines the efficacy of a new experimental treatment method. The purpose of this consent form is to provide you with the information that you will need to help decide if you would like to participate in this experimental study. Please read the form carefully. You may ask questions about the purpose of the research, such as what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that may be unclear to you. When we have answered all your questions, you can decide whether or not you would like to participate. This process is called "informed consent". We will provide you a copy of this form for your records.

PURPOSE OF THE STUDY

Epilepsy is a disease that involves persistent abnormal electrical activity in various, but sometimes specific, parts of the brain. These abnormalities can be seen in forms of epileptic seizures and/or interictal spike discharges. "Interictal" specifically refers to the period of time between your seizures; it is during this time that small "spikes" of electricity are most active in your brain.

Scientists have found that these spikes can be reduced or even stopped through slow, pulsed, electrical stimulation, otherwise known as transcranial pulsed current stimulation (tPCS). What this means is that short, small, periodic pulses of electricity delivered to the parts of your brain where these spikes occur, might suppress them or even prevent them from occurring in the future. Quite a few treatments that rely on similar principles have already been developed, but until now they have been either extremely invasive, involving the surgical implantation of hardware directly into the brain, or not very effective. We would like to try a new experimental

treatment method. What will potentially set this method apart is that it is entirely non-invasive and many of the problems affecting the other non-invasive therapies, we believe, have been solved.

STUDY SUMMARY

This study is an unblinded "open-label" experimental study. If you participate, you will have a total of 14 visits and up to weekly phone calls. The focus of this study is the evaluation of the safety, feasibility, and efficacy of our new experimental treatment method. This method is non-invasive epilepsy treatment by means of slow-pulsed electrical stimulation or "modulation". If you choose to participate, we ask that you to continue taking your anti-epileptic medication throughout the entirety of this study. In addition, due to the experimental nature of this treatment, if you are a woman of childbearing capability, use of a form of birth control throughout the entirety of the study will be required. If at any point during the study you become or think you have become pregnant your participation must be discontinued.

The first step of your participation will be to establish a baseline of your epileptic spike activity. In order to establish this baseline, it will be necessary that you come in for two 1-3 hour baseline dense array EEG (dEEG) recording sessions over the course of two months. You will come to the Regional Epilepsy Center for an outpatient research appointment where the assistant investigator will place an elastomer net of electrodes on your head; this will allow us to record your interictal spike activity. We will take several pictures of the net one your head, which we will use along with your individual MRI to build a 3D computer head model specific to your own brain and skull. If you have never had an MRI before as part of your normal clinical care, the lead investigator will request that you have one performed. Once we have applied the net and taken your images, you will rest in a bed as we record your epileptic brain activity with the dEEG system.

At the beginning of this study you will be given a seizure diary with daily use instructions. Each page of the seizure diary has a series of questions we'd like you to answer every day for the duration of this study. During the baseline stage, and for the rest of the study, you will receive monthly phone calls or emails from one of the investigators to ask about your seizure activity. It is important for us to know about all of the seizures you may or may not be having during this time so that after treatment we can evaluate the effectiveness of the therapy.

Once you have completed two baseline recordings, we will analyze your dEEG data with your 3D brain model to identify a dominant target(s) of your epilepsy. This will allow us to generate two treatment plans for this target. Before we continue on to your experimental treatment, two experimental probe test treatment sessions must be completed to determine which of the two treatment plans will be the most effective for your target(s). After the experimental probe test treatments have been executed and evaluated, you will come in five consecutive days for the experimental stimulation treatment sessions. These sessions will last anywhere from two and a half hours to five hours, with the duration depending on whether your seizures occur more typically around sleep or around wakefulness, as well as which day of the treatment you are in.

After you have completed the five days of experimental stimulation treatment, you will begin a six-month long period of follow-up sessions so that we can evaluate how the treatment has

worked for you. You will come in at 2, 4, 8, 16, and 24 weeks following the experimental treatment. These follow-up sessions will all be identical. You will be asked to complete two cognitive tests to assess your memory function and quality of life; these tests are the California Verbal Learning Test and the Quality of Life in Epilepsy questionnaire. You will also be asked to have 30-120 minutes of dEEG recording to monitor your post-treatment epileptic activity. The length of these recordings will once again depend on whether or not you will need to be asleep. Only after all of the follow-up has been completed will we know whether or not the treatment has been effective for you.

STUDY PROCEDURES

As mentioned above, the study will begin with a baseline component. During this stage you will come into the Harborview Regional Epilepsy Center twice, over the course of two months, for two 1-3 hour dEEG recording sessions. This component will be necessary for us to better understand your epilepsy and your epileptic interictal spikes, which in turn will help us in evaluating the efficacy of this experimental treatment method.

A second aspect of this baseline component will be the monthly phone interviews or email communications you receive from a member of the research team to briefly summarize your most recent entries into your seizure diary. After treatment, these diaries will be extremely helpful when evaluating if the treatment has had an effect on your seizure frequency. You may or may not already be completing a seizure diary as part of your clinical care, but either way we will provide you with one for this study and teach you how to fill it out correctly. You will also complete the Quality of Life in Epilepsy Questionnaire and the California Verbal Learning Test during your first baseline session. These tests will allow us to observe if the experimental stimulation treatment has caused any changes in your quality of life or cognitive functioning.

After you have completed the baseline stage, we will analyze and identify your potential treatment target(s). Your treatment target(s) will be identified and localized by means of your dominant interictal spike group that we recorded in the baseline dEEG sessions and your individual 3D head model we will have generated from the images we took of the net on your head. With this information, we would like to run two experimental probe test treatment sessions to stimulate your proposed treatment target area(s) in two different ways. The probe tests will start with a 1-hour dEEG monitoring session followed by a 17-minute experimental stimulation treatment session (500 slow electrical pulses), which will then be followed immediately by one more 1-3 hour dEEG monitoring session. The format of this experimental probe test will allow us to determine and confirm which of the proposed target area plans will be your final and most accurate treatment plan. These tests will also allow us to ensure that there is no worsening of your epilepsy from the experimental stimulation. If one of the probe tests is successful and discharges are suppressed, we will be ready to schedule your treatment sessions.

The experimental probe test and experimental treatment stimulation sessions will go as follows; you will first have a dEEG electrode net placed on your head in a way that exactly matches how we have applied it to your head in the baseline sessions, we will do this with the images we took of you previously. After the net has been applied, we will use your treatment plan to guide us as we fill each of the 256 scalp electrodes with either an electrolyte paste called Elefix or with a

mixture of this same Elefix paste with topical lidocaine, "Topicaine®". The lidocaine mixture is meant to ensure your own comfort during the experimental treatment, as the small electrical current pulses can be slightly irritating to the skin. We will then take another picture of the net on your head to verify electrode placement. Once these steps are complete, we will plug the dEEG electrode net into our experimental treatment device, the Geodesic Transcranial Electrical Neuromodulation amplifier, or GTEN 100.

This experimental treatment system is a slightly modified dEEG amplifier system. Normally, a dEEG amplifier will simply transfer the signals of the dEEG back to the computer. What the GTEN 100 amplifier system does is slightly different, but still straightforward. Using the information we have gathered from your baseline recordings and thus the treatment plan we have created from said information, the GTEN 100 amplifier will send very small electrical currents through the electrode net to the part of your brain that we have identified as your treatment target. At the same time the system will also record and monitor the activity coming from all other areas of your brain. This simultaneous dEEG recording will allow us to monitor any potential seizure activity that may be occurring during your experimental stimulation treatment.

Before both the experimental probe test and experimental GTEN 100 treatment begins, we will have you lay down for 10 minutes of what is called "Resting dEEG". This consists of you relaxing with your eyes open for one minute and closed for the next until the 10 minutes it over. We do this to make sure that the net has been applied properly and that all the equipment is working well. While the resting dEEG is being recorded, we will begin what is called "iontophoresis". What this means is that we will use unnoticeable amounts of electrical current to pass ions through your scalp. This process will help to move the topical lidocaine into your scalp for faster absorption. Topical lidocaine is a widely used local anesthetic that you might have had used on you before, perhaps at the dentist or after a sunburn. This lidocaine will be mixed into the Elefix paste and filled into the specific current injection electrodes for your treatment plan. In doing this we will help to ensure that the experimental stimulation treatment you receive will be as comfortable for you as possible.

Once the resting dEEG has been completed, the experimental GTEN modulation will begin. The experimental probe test modulation will proceed as mentioned previously with one 17-minute block of stimulation, where as the experimental GTEN treatment will proceed as follows; for three sets of 17 minute blocks, every two seconds an electrical pulse lasting one tenth of a second will be sent from the electrodes on your scalp to your treatment target in your brain. Each modulation session of the 5-day treatment section will last a little more than 90 minutes, involving three stimulation blocks separated by two 10-minute rest periods. All you will need to do during the entire treatment is sit or sleep passively.

Please note that the current pulses you receive can be slightly irritating and can produce some minor tingling, poking, or itching sensations on your scalp. Preliminary studies do indicate that the application and absorption of lidocaine on to your scalp will prevent the experimental GTEN stimulation from being too painful, which is why we have applied lidocaine to your current injection electrodes. However, always keep the fact in mind that you can elect to halt the stimulation, and the study in its entirety, whenever you would like to if you feel the need to do so.

After the three experimental GTEN stimulation blocks are complete for the day, we will begin a 1-3hr dEEG recording. The length of this recording will depend on which day of treatment you are in. The first day of the experimental treatment will be followed by a 3hr dEEG and each of the four following experimental treatment days will be followed by at least 1 hour of dEEG. Each dEEG recording following your experimental stimulation, especially for treatment 1, will be important for yourself and for the study as our goal is to monitor any potential changes of your epileptic activity as a result of the experimental GTEN modulation.

Once the 5 days of experimental GTEN treatment are complete, you will begin a 6-month follow-up segment. You will be asked to attend a follow-up session at 2, 4, 8, 16, and 24 weeks post-treatment. In each follow-up session you will complete a dEEG recording, the California Verbal Learning Test, and the Quality of Life in Epilepsy Questionnaire. An investigator will also call you once a week to go through your seizure diary with you. All of the follow up sessions that you will attend after the 5 days of experimental GTEN treatment will be identical. As stated previously, we are doing these follow-up sessions to make sure you're doing well and to see if the GTEN modulation has had a beneficial effect on your epileptic activity.

For the purposes of this project, we would like to record the following information from your medical record: your age and sex, information about your epilepsy, dEEG results, and other images such as MRI and/or CT. We would like to record information from your medical record until December 19, 2019.

RISKS, STRESS, OR DISCOMFORT

Questionnaires and general risks:

- There are many questionnaires. These present a risk of loss of privacy. There is also a risk that you may be uncomfortable about the questions.
- An unauthorized person could access your information. We do however have procedures in place to prevent this from happening.
- You could experience psychological distress if you do not notice any positive changes from the study. We ask that you keep in mind the fact that this is an experimental safety and feasibility trial and that there is a chance that you will not benefit from participating in this study.
- If you suffer from eczema on your face, you may experience skin irritation or an eczema flare from the sensor net, elefix paste, lidocaine topical gel, and/or electrical stimulation.

Iontopheresis risks:

- If you are allergic to silver, this procedure could trigger an allergic reaction as the electrodes are plated with a Silver/Silver Chloride. Please tell us now if you are allergic to silver.
- If you are allergic to topical lidocaine anesthetic, this procedure could trigger an allergic reaction such as skin irritation. Please tell us now if you are allergic to lidocaine.

Stimulation session risks

- Procedures involving the GTEN device may involve risks that are currently unforeseeable.
- During each electrical pulse of stimulation you could experience a feeling of tingling, itching, needle poking, and/or discomfort on your scalp.

- During each electrical pulse of stimulation you could also experience vision changes such as light flashes or phosphenes (a ring or spot of light).
- It's also possible that you could experience fatigue, nausea, dizziness, burning, headaches, or a skin reaction such as dryness, redness, or itching.
- There is a very slight, but still possible chance that the experimental stimulation could cause you to experience more seizures. These seizures could be different than your usual seizures. The experimental probe test treatment sessions will let us know if this is likely to occur in your therapy session.
- If you are pregnant and have a seizure, it could lead to early labor. To prevent this risk, if there is a chance you could be pregnant we will ask you to take a urine pregnancy test before starting the study. If the test is positive, you will not be allowed to take part in the study.
- There is a potential risk that you may not benefit from this experimental treatment.

BENEFITS OF THE STUDY

THERE MAY BE NO BENEFIT TO YOU IN PARTICIPATING IN THIS STUDY

There is a chance that you may experience a reduction in your epilepsy-related symptoms (fewer seizures, better cognitive functioning, etc.). However, this is part of an experimental, safety and feasibility trial and you may not benefit personally from participating in this study. The GTEN 100 device used in this study has been approved by the FDA for investigational purposes only and has not yet been approved for clinical use. Individuals, including yourself, in the future may very well benefit from the information obtained in this study, but there is a chance that you may not.

SOURCE OF FUNDING

The investigators of this study, Dr. Mark Holmes and Mackenzie Wise, are receiving payment from the study sponsor, Philips-Electrical Geodesics Inc. (Philips-EGI), for the time spent running patients through the study, evaluating patient dEEG, and recruiting patients to participate in this study. Philips-EGI is also providing the equipment and study materials that will be used throughout this study. The University of Washington is receiving payment from Philips-EGI for use of its facilities.

CONFIDENTIALITY OF RESEARCH INFORMATION

The data collected in this study will be confidential. The identifiers that will be used to link your name with the data we collect will be broken at the end of the study so that the data will still be useable but nobody will be able to link it to you.

If you decide to stop being in the study, or are removed from the study, or the study is stopped, the data collected about you up to that point will remain part of the study and may not be removed from the study database.

Government or university staff will periodically review this study to make sure all study practices are being done safely and legally. When a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. The U.S. Food and Drug Administration (FDA) reserve the right to review study data that may contain identifying information.

ALTERNATIVE TO TAKING PART IN THIS STUDY

Alternatives to this study include continuing on with your regular clinical care. Your clinical care will not be affected in any way by your agreement or refusal to take part in this study and you may elect to end your participation at any time.

OTHER INFORMATION

Taking part in this study is voluntary. Participation in this study will last between 9 months to one year. You may refuse to participate and you are free to withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled. To withdraw from this study, simply contact a member of the research team and inform he/she that you would like to withdraw. The contact information for the research team members can be found at the beginning of this consent form.

The FDA has asked us to inform you that new significant research findings may develop during the course of your participation that may affect your willingness to participate. If such circumstances arise, we will inform you of the new findings and will provide you with time to reconsider your enrollment in the study.

Any study related injury, if not immediately treatable by Dr. Mark Holmes will be charged to you or your insurance (see below). We will compensate you for your participation and for incurred expenses accrued from time spent in the sessions of this trial. We will compensate you at a rate of $50 per session after the baseline component has been completed (i.e., probe test sessions, treatment sessions, follow-up sessions).

The components of the study that will be covered by the study will include:

- Seizure diaries
- dEEG recordings during baseline sessions, experimental probe test treatment sessions, experimental GTEN stimulation and each follow-up session
- GPS image acquisitions
- Experimental Probe test GTEN treatment stimulation
- Experimental GTEN treatment stimulation
- California Verbal Learning Tests (CVLT)
- Quality of Life in Epilepsy Questionnaires (QOLIE)
- Monthly phone calls or emails for general health and seizure diary review
- Incurred Costs up to $50/session (I.e. parking, transportation costs)

Possible necessary services not covered by the study might include:

- Study-related injury treatment (see below)
- Transportation
- Lodging if necessary

RESEARCH RELATED INJURY

What to do. For a life-threatening problem, call 911 right away or seek help immediately. Contact Dr. Mark Holmes (206-744-3576) when the medical emergency is over or as soon as you can. For all other problems: contact Dr. Mark Holmes (206-744-3576) right away. He will treat you or refer you for treatment.

Who will pay. The costs of the treatment may be billed to you or your health insurance just like other medical costs, or it may be covered by the UW's discretionary Human Subjects Assistance Program (HSAP), depending on a number of factors. The investigator may request HSAP coverage by following established procedures. If you wish to request HSAP coverage yourself, contact the investigator or the UW Human Subjects Division at hsdinfo@uw.edu or 206-543-0098. Ask the investigator if you would like information about the limits and conditions of the HSAP. The UW does not normally provide any other form of compensation for injury. However, the law may allow you to seek payment for injury-related expenses if they are caused by malpractice or the fault of the investigators. You do not waive any right to seek payment by signing this consent form. We will bill your health insurance for treating problems that result from your epilepsy or from standard clinical care. If you have no health insurance or your insurance refuses to pay, we will bill you.

Printed name of study staff obtaining consent Signature Date

Subject's statement

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, I can ask one of the researchers listed above. If I have questions about my rights as a research subject, I can call the Human Subjects Division at (206) 543-0098. I give permission to the researchers to use my medical records as described in this consent form. I will receive a copy of this consent form.

Printed name of subject Signature of subject Date

Session	Procedure
Pre-Evaluation	- Review of seizure diary each week for two months. - Two 1-3 hour clinical dEEG evaluations to capture epileptiform discharges (ED), including spikes and seizures. - MRI when available to determine possible malformations of cortical development and build individual head model. - bEIT scan to verify electrical head model. Lidocaine iontophoresis conditioning during this scan. - Two 17 minute experimental tPCS probe test (500 pulses) to seizure onset zone to test target area and treatment plan. (Sessions must be at least two days apart).
First Treatment Session	- Review of seizure diary. - Application of the Geodesic Sensor Net. - Geodesic Photogrammetry System (GPS) to localize sensors. -10 minutes resting clinical dEEG. Lidocaine iontophoresis conditioning during this scan. - Experimental GTEN treatment: 3 sets of 500 pulses (600s intervals between sets) or 3 sets of sustained tDCS with the same intervals. - 180 minutes resting clinical dEEG (regulatory to monitor seizure activity) - California Verbal Learning Test - Quality of Life in Epilepsy Questionnaire
Treatment Sessions 2-5	- Review of seizure diary. - Application of the Geodesic Sensor Net. - Geodesic Photogrammetry System to localize sensors. - 10 minutes resting clinical dEEG. Lidocaine iontophoresis conditioning during this time. - Experimental GTEN treatment, 3 sets of 500 pulses (600s intervals between sets) or 3 sets of sustained tDCS with the same intervals. - 60 minutes resting clinical dEEG (unless sleep EEG needed, then up to 2 hrs). - California Verbal Learning Test - Quality of Life in Epilepsy Questionnaire
Follow-Up Sessions: weeks 2, 4, 8, 16, and 24	- Review of seizure diary. - Application of the Geodesic Sensor Net. - Geodesic Photogrammetry System to localize sensors. - 30-120 minutes resting dEEG (unless sleep EEG needed, then up to 2 hrs).

	• California Verbal Learning Test • Quality of Life in Epilepsy Questionnaire

Table 1: Summary of Treatments and assessments